Age, Cohort-of-Birth, and Period-of-Death Trends in Breast Cancer Mortality in Europe

An age-period and cohort model fit to breast cancer mortality data in the United States and Canada showed downward shifts in slopes of cohort effects for white women born after 1925 and for period-of-death values from 1970 onward (*1*).

We applied an age-period and cohort model to European breast cancer mortality data. Briefly, official cancer death certification numbers for 16 major European countries during the period 1955-1994 were derived from the World Health Organization (WHO) database (*2*). Estimates of the resident population, generally based on official censuses, were obtained from the same WHO database. From these data, age-specific death certification rates for each 5-year calendar period and age group (from 30-34 years to 75-79 years) were derived.

From the matrices of age-specific death rates, the effects of age, cohort of birth, and period of death were estimated through a log-linear Poisson model, fitted using GLIM with appropriate user-supplied macros (*3*). In simplified terms, the estimates presented are derived from the model including the three factors (age, cohort, and period), which minimizes the sum of the Euclidean distances from the three possible two-factor models (age and period, age and cohort, or cohort and period). The procedure is conceptually similar to that described by Osmond and Gardner (*4*). The age values are interpretable in terms of mean age-specific death rates in the period considered. Cohort and period-of-death values were averaged to unity. Cohort values related to earlier and more recent periods are based on fewer age-specific rates and, hence, are less reliable than central ones.

Fig. 1 gives the age, cohort, and period values for breast cancer mortality in the 16 major European countries consid-

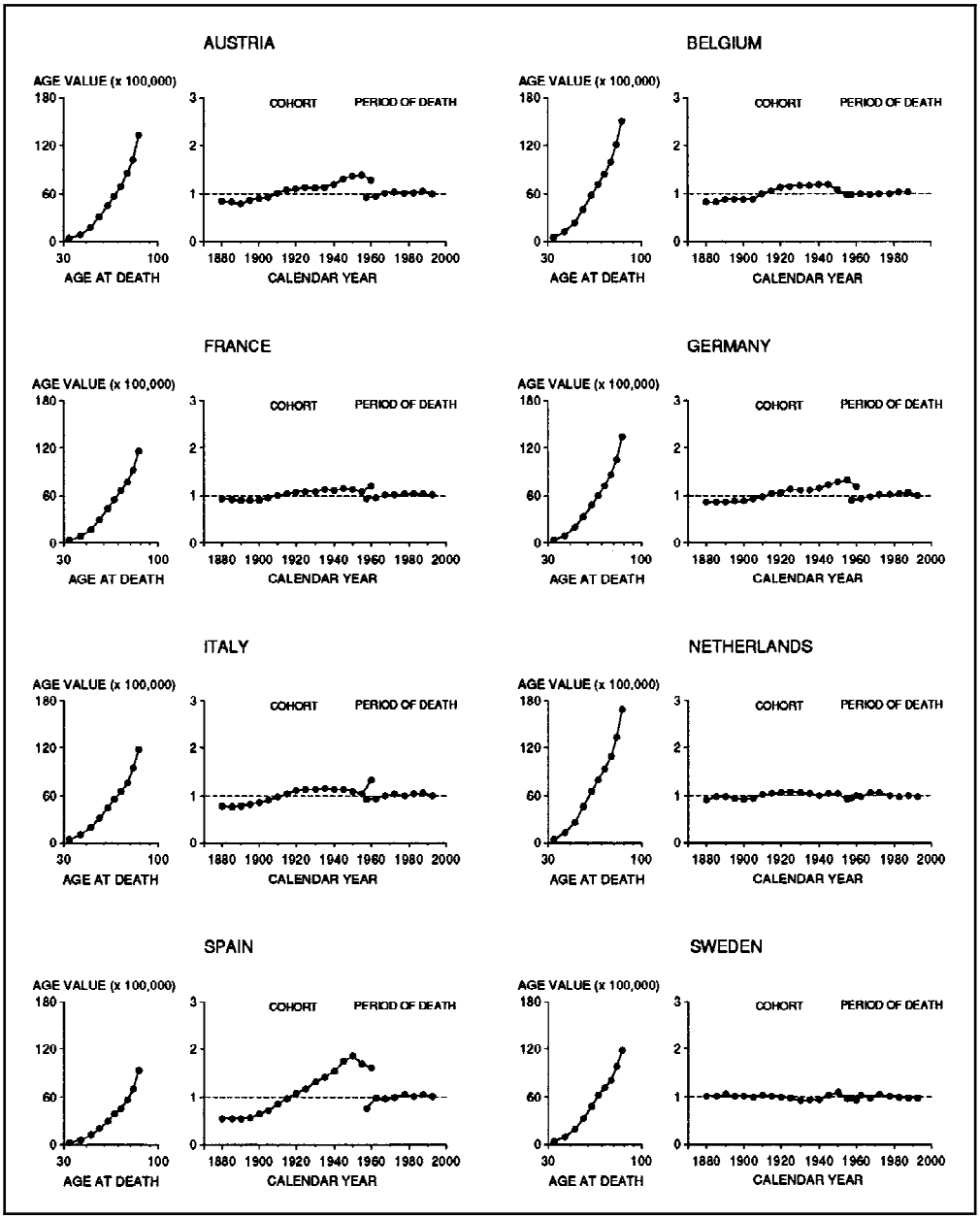


Fig. 1 (*see* facing page also). Age, cohort, and period effects for breast cancer mortality in women in selected European countries. The age effect can be interpreted in terms of rates per 100 000 population. Cohort and period-of-death effects are expressed in relative terms against their weighted average set to unity.

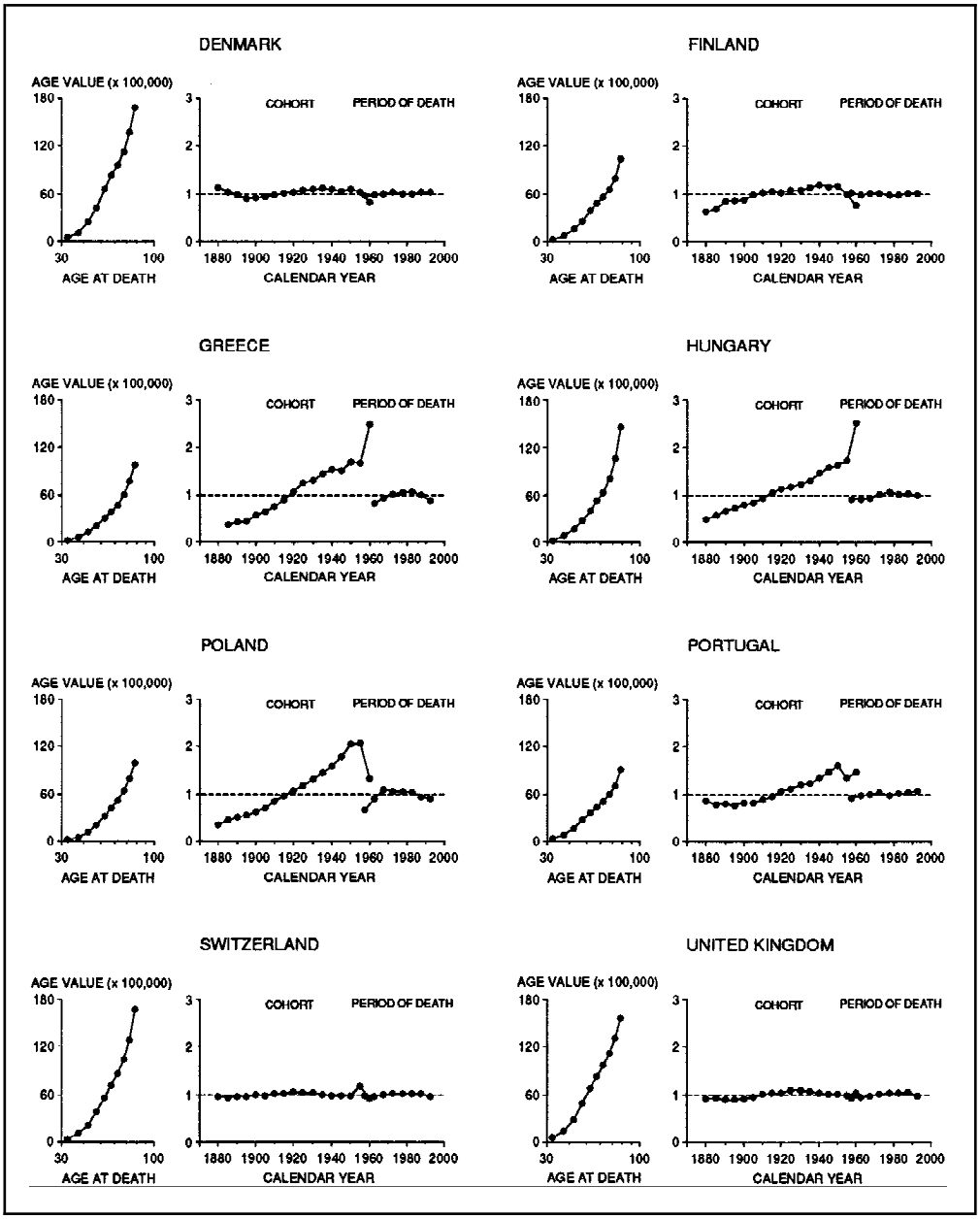
ered. Age values tended to be higher in northern Europe and lower in southern and eastern European countries. Cohort values showed two patterns, since most northern European countries showed no noteworthy trend, while there were appreciable increases for cohort values in Spain, Portugal, Greece, Hungary, and Poland as well as a small increase in Italy. Period-of-death values were stable in most countries.

It seems, therefore, that subsequent generations of women from originally low-risk European countries had experienced increased breast cancer mortality, thus leading to a leveling of breast cancer death rates across Europe. This finding probably reflects more uniform reproductive, hormonal, and perhaps dietary factor exposures among younger women in various European countries (*2*,*5*,*6*).

These figures are not directly comparable to those given by the model applied by Tarone et al. (*1*), which considered changes in slopes. In terms of changes in slopes, several European countries showed downward shifts for most recent generations, and some of them, including the largest ones (i.e., France, Germany, Italy, and the U.K.), also showed downward shifts for most recent periods of death.

Nonetheless, the fall in breast cancer rates observed over recent calendar periods and cohort of births in North American white women (*1*) was only partly reproduced in Europe. This result suggests that there are differences and specificities in reproductive variables and exposures to other likely risk factors, as well as in early diagnosis (*7*) and management of the disease, in various developed areas of the world. Furthermore, an appreciable heterogeneity was observed in breast cancer mortality across various European countries and geographic areas (*6*,*8*), whose determinants should be further investigated.

CARLO LA VECCHIA
EVA NEGRI
FABIO LEVI
ADRIANO DECARLI



References

(*1*) Tarone RE, Chu KC, Gaudette LA. Birth cohort and calendar period trends in breast cancer mortality in the United States and Canada. J Natl Cancer Inst 1997;89:251-6.

(*2*) La Vecchia C, Lucchini F, Negri E, Boyle P, Maisonneuve P, Levi F. Trends of cancer mortality in Europe, 1955-1989: III. Breast and genital sites. Eur J Cancer 1992; 28A:927-98.

(*3*) Decarli A, La Vecchia C. Age, period and cohort models: review of knowledge and implementation in GLIM. Rivista Statistica Applicata 1987;20:397-410.

(*4*) Osmond C, Gardner MJ. Age, period and cohort models applied to cancer mortality rates. Stat Med 1982;1:245-59.

(*5*) Willett W. The search for the causes of breast and colon cancer. Nature 1989;338:389-94.

(*6*) Hermon C, Beral V. Breast cancer mortality rates are levelling off or beginning to decline in many western countries: analysis of time trends, age-cohort and age-period models of breast cancer mortality in 20 countries. Br J Cancer 1996;73:955-60.

(*7*) Levi F, Te VC, La Vecchia C. Impact of mammography on breast cancer incidence in Vaud, Switzerland [letter]. J Natl Cancer Inst 1991;83:1181-2.

(*8*) Caygill CP, Hill MJ. Trends in European breast cancer incidence and possible etiology. Tumori 1991;77: 126-9.

Notes

Affiliations of authors: C. La Vecchia, Istituto di Ricerche Farmacologiche ''Mario Negri'' and Istituto di Sta-

tistica Medica e Biometria, Università degli Studi di Milano, Milan, Italy; E. Negri, Istituto di Ricerche Farmacologiche ''Mario Negri''; F. Levi, Registre Vaudois des Tumeurs, Institut Universitaire de Médecine Sociale et Préventive, Lausanne, Switzerland; A. Decarli, Istituto di Statistica Medica e Biometria, Università degli Studi di Milano.

Correspondence to: Carlo La Vecchia, M.D., Istituto di Ricerche Farmacologiche ''Mario Negri,'' via Eritrea 62, 20157 Milano, Italy.

Conducted within the framework of the Italian National Research Council (CNR) Applied Project ''Clinical Applications of Oncological Research'' (Contracts No. 96.00548.PF39 and 96.00759.PF39) and with the contributions of the Italian Association for Cancer Research and the Italian and Swiss Leagues Against Cancer, Milan and Bern.

Re: Monitoring of Aromatic Amine Exposures in Workers at a Chemical Plant With a Known Bladder Cancer Excess

In 1991, investigators from the National Institute for Occupational Safety and Health (NIOSH) (*1*) reported a correlation between *o*-toluidine and aniline exposure and an increased incidence of bladder cancer. Letters published in the Journal (*2-4*) identified deficiencies and inaccuracies in the study. The recent article by investigators from NIOSH (*5*) continues the inaccurate portrayal of *o*-toluidine and aniline as human bladder carcinogens.

The bladder cancers were diagnosed in the early 1980s. Since the latent period between exposure and tumor expression averages about 20 years, NIOSH should have examined worker exposure to chemicals used in the early 1960s, but it did not do so. The article (*5*) states, ''There were insufficient historical data to characterize exposures at the plant 10-30 years ago, the time period most relevant to the development of industrially related bladder cancers, which have a latent period . . . averaging 20 years. . . .'' Therefore, NIOSH admits it has no knowledge of the specific chemicals to which the affected workers were exposed. NIOSH also admits that exposures 10-30 years ago are most relevant to causation but ignores historical exposure information.

There is documentation that workers were exposed in the 1950s and early 1960s to diphenylamine. Diphenylamine often contained 4-aminobiphenyl, a known human bladder carcinogen (*6*). NIOSH admits the possibility of exposure to 4-aminobiphenyl from contact with process chemicals but dismisses 4-aminobiphenyl as a causative agent.

Donald Sherman, M.D., Corporate Medical Director for the affected plant, informed NIOSH that 4-aminobiphenyl was present in the plant from 1957 to mid-1966. He stated that no worker with a start date after 1966 has developed bladder cancer. Dr. Sherman states, ''We have believed all along that aniline and *o*-toluidine did not cause the cancers in the Niagara Falls plant. . . . The exposures to aniline and *o*-toluidine from 1966 to the late 1970s did not change significantly, based upon process design and configuration. If *o*-toluidine was the real culprit . . . would we not have seen more bladder cancers? . . . We believe the probable cause was 4-aminobiphenyl. . . .'' (Sherman DJ: personal communication to Ward JM, May 23, 1996). This confirmation that workers with bladder cancer were exposed to 4-aminobiphenyl invalidates the conclusions of the NIOSH study that used exposure data from the late 1980s.

NIOSH reported workplace air concentrations of 187 and 412 $\mu g/m^3$ for aniline and *o*-toluidine, respectively, orders of magnitude below the Occupational Safety and Health Administration Permissible Exposure Limits (PELs) of 8000 and 22 000 $\mu g/m^3$ and the American Conference of Governmental Industrial Hygienists (ACGIH) Threshold Limit Values (TLVs) of 7600 and 8800 $\mu g/m^3$, the concentrations to which workers can be exposed 8 hours per day, 5 days per week, for 30 years without adverse health effects. Furthermore, in 1996, the ACGIH downgraded the classification of aniline and *o*-toluidine from ''suspected human carcinogen'' to ''animal carcinogen.'' NIOSH apparently refutes the validity of TLVs and PELs as universally accepted safe exposure levels.

There are no data in Ward et al. (*5*) that support the NIOSH conclusion that ''. . . occupational exposure to *o*-toluidine is the most likely cause of the bladder cancer excess observed among workers in the . . . plant under study. . . .''

RALPH I. FREUDENTHAL
DANIEL P. ANDERSON

References

(*1*) Ward E, Carpenter A, Markowitz S, Roberts D, Halperin W. Excess number of bladder cancers in workers exposed to ortho-toluidine and aniline. J Natl Cancer Inst 1991;83:501-6.
(*2*) Tannenbaum SR. Bladder cancer in workers exposed to aniline [letter]. J Natl Cancer Inst 1991;83:1507-8.
(*3*) Freudenthal RI, Anderson DP. A re-examination of the cause of excess bladder cancers in chemical plant workers [letter]. J Natl Cancer Inst 1994;86:59-62.
(*4*) Acquavella JF, Wilson JD, Conner P, Bannister R. An alternative hypothesis for bladder cancer among workers exposed to ortho-toluidine and aniline [letter]. J Natl Cancer Inst 1991;83:1686-7.
(*5*) Ward E, Sabbioni G, DeBord DG, Teass AW, Brown KK, Talaska GG, et al. Monitoring of aromatic amine exposures in workers at a chemical plant with a known bladder cancer excess. J Natl Cancer Inst 1996;88:1046-52.
(*6*) Safe S, Hutzinger O, Crocker JF, Digout SC. Identification of toxic impurities in commercial diphenylamine. Bull Environ Contam Toxicol 1977;17:204-7.

Notes

Affiliations of authors: R. I. Freudenthal, Consultant, Toxicology and Regulatory Affairs, Palm Beach, FL; D. P. Anderson, Environmental Affairs, First Mississippi Corporation, Pascagoula, MS.

Correspondence to: Ralph I. Freudenthal, Ph.D., 8737 Estate Drive, West Palm Beach, FL 33411.

R. I. Freudenthal is a consultant in the field of toxicology to First Chemical Corporation; Daniel P. Anderson is Vice President of the First Mississippi Corporation, parent company of First Chemical Corporation, a manufacturer of aniline and *o*-toluidine.

Ward et al. (*1*) recently presented the results of biologic monitoring of workers for aromatic amine exposure in a chemical plant. They concluded that exposure to *o*-toluidine is the most likely cause of the excess numbers of bladder cancers found in the study population and noted that exposure to aniline cannot be ruled out as a potential cause. This article follows an earlier study in which they found an excess of bladder cancer at the plant (*2*).

Several articles (*3-8*) have linked source of drinking water, total fluid intake, water disinfection methods, or exposure to chlorinated surface water with bladder cancer. Four of these articles (*5-8*) were published before Ward et al.